

REMARKS

Claims 1-37 were pending in the instant Application. With the instant amendment, Applicants have amended claim 31 without narrowing its scope. Support for amended claim 31 can be found in the specification at, for example, the bottom of page 26 through the middle of page 30 (paragraphs 188-221 of U.S. Publication No. 2002/0058262 A1). After entry of this amendment, claims 1-37 remain pending. Applicants expressly reserve the right to pursue any canceled subject matter in one or more related, continuation, divisional or continuation-in-part application(s).

Applicants would like to inform the PTO that another application by the same inventors, U.S. Patent Application No. 09/823,711, Attorney Docket No.: 5394 (1803-284-999), Confirmation No.: 7442, was filed on March 30, 2001.

I. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 31-37 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants possessed the claimed invention. The PTO alleges that the negative limitation, “but need not be,” raises a written description issue under 35 U.S.C. § 112. Although Applicants maintain that the subject matter of claims 31-37 is sufficiently described by the specification, Applicants have amended claim 31 merely to expedite prosecution and secure rapid allowance of the claims by deleting the phrase. Applicants submit that the amendment of claim 31 obviates the PTO’s rejection of claims 31-37.

In view of the foregoing, Applicants respectfully request that the rejection of claims 31-37 under 35 U.S.C. § 112, first paragraph, be withdrawn.

II. THE REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-30 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Wittwer *et al.*, 2001 (U.S. Patent No. 6,232,079, “Wittwer”) in view of Brown *et al.*, 2000 (U.S. Patent No. 6,143,496, “Brown”). Applicants traverse this rejection on the grounds that the references cited by the PTO are not sufficient to establish a *prima facie* case of obviousness against any of the claims.

A. The Legal Standard

To reject claims in an application under 35 U.S.C. § 103, the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. In the absence of establishing a proper *prima facie* case of obviousness, applicants who comply with the other statutory requirements are entitled to a patent. *In re Oetiker*, 24 USPQ2d. 1443, 1444 (Fed. Cir. 1992). In order to establish *prima facie* obviousness, three basic criteria must be met.

First, the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the PTO to arrive at the claimed invention. When an obviousness determination relies on one reference, there must be suggestion or motivation to modify the teaching of the reference in the manner suggested by the PTO. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). Alternatively, when an obviousness determination relies on a combination of two or more references, there must be some suggestion or motivation to combine the references. *WMS Gaming Inc. v. International Game Technology*, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). The suggestion or motivation to combine the references generally arises in the references themselves, but may also be inferred from the nature of the problem or occasionally from the knowledge of those of ordinary skill in the art. *See id.* The mere fact that references could be modified or combined does not render the resultant modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01.

Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. Thus, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the PTO would succeed. *In re Dow*, 5 USPQ2d 1529, 1531 32 (Fed. Cir. 1988).

Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Gartside*, 53 USPQ2d 1769 (Fed. Cir. 2000). The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). If any one of these criteria are not met, *prima facie* obviousness is not established, and Applicants are not required to show new or unanticipated results. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985).

Further, the PTO may not establish a *prima facie* case of obviousness based on inherency. Consideration of inherency is not relevant to obviousness; it is only relevant to anticipation. *Jones v. Hardy*, 220 USPQ 1021, 1025 (Fed. Cir. 1984) (stating that the lower court's conclusion "confuses anticipation by inherency, *i.e.*, lack of novelty, with obviousness, which . . . are separate and distinct concepts."). In *In re Newell*, the court held that "a retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination." *In re Newell*, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989). Further, it held "[t]hat which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *Id.* at 1250; *see also In re Naylor*, 152 USPQ 106, 108 (CCPA, 1966).

B. Wittwer and Brown, Alone or in Combination, Do Not Teach or Suggest Each and Every Element of Claims 1-30

Applicants respectfully submit that the references cited by the PTO are not sufficient to establish a *prima facie* case of obviousness against claims 1-30 because neither Wittwer nor Brown, alone or in combination, teaches or suggests each and every element of claims 1-30. For convenience, Sections 1 and 2 below discuss the reasons why claims 1-8, 15, 18-30 and claims 9-14, 16-17, respectively, are not obviated by the combination of Wittwer and Brown.

1. Wittwer and Brown, Alone or in Combination, do not Teach or Suggest Each and Every Element of Claims 1-8, 15 and 18-30

Independent claims 1 and 18 recite methods of determining amplification efficiency of a target nucleic acid as a function of the amount of target nucleic acid where, *inter alia*, the cycle number at which amplification, as measured in real-time, exceeds a threshold is determined for dilutions of the nucleic acid. Claims 2-8 and 15 depend from claim 1 and claims 19-30 depend from claim 18.

Wittwer does not teach or suggest each and every element of independent claims 1 or 18. First, independent claims 1 and 18 recite a method of determining amplification efficiency as a function of the amount of target nucleic acid. Wittwer does not teach or suggest a method of determining amplification efficiency as a function of the amount of target nucleic acid. Instead, Wittwer merely states that "amplification efficiency can be rigorously determined by integrating the melting peak data" (*see example 19, column 41, lines 43-46*). Applicants submit that a mere statement that "amplification efficiency can be determined," without further elaboration, neither teaches nor suggests a method for

determining amplification efficiency. Wittwer does not teach any steps, formula, procedure etc. for actually determining amplification efficiency from melting peak data. Accordingly, Wittwer does not teach a method for determining amplification efficiency. Applicants submit that Wittwer may, at best, suggest that the differences in the areas under the melting peaks of, for example, CFTR and neu, may be indicative of differences in their amplification efficiencies (*see* figure 44).

Further, although Wittwer points to example 16 as teaching a method for determining amplification efficiency, example 16 does not teach or suggest a method of determining amplification efficiency. In fact, example 16 does not even contain the phrase “amplification efficiency.” Instead, example 16 teaches a method of converting melting curves to melting peaks so that the “area under the melting peaks can . . . be quantified by integration of the area under the curves” (*see* Wittwer, column 39, lines 35-36). Thus, example 16 may teach that the area under the melting peak is indicative of the *quantity* of nucleic acid present in the sample, however, it does not teach or suggest a method for determining amplification efficiency.

Even assuming *arguendo*, that the brief statement that “amplification efficiency can be determined” of example 19 and its reference to example 16 do suggest any method for determination of amplification efficiency, which they do not, then they, at best, suggest the determination of amplification efficiency from a melting curve analysis; *i.e.*, from a plot of fluorescence versus temperature. Such an analysis in no way teaches or suggests a method of determining amplification efficiency as a function of the amount of nucleic acid or a method of determining amplification efficiency based on the determination of a cycle number at which a threshold is exceeded.

Next, independent claims 1 and 18 recite determination of a cycle number at which amplification exceeds a threshold. Wittwer does not teach or suggest determination of a cycle number at which a threshold is exceeded. In fact, Wittwer *teaches away* from determining a cycle number at which a threshold is exceeded (*see* column 33, lines 22-31). Column 33, lines 22-31 of Wittwer teach the disadvantages of choosing “a ‘threshold value’ of the signal and then [using] the cycle number when the standard or unknown crosses that threshold.” It teaches that “[t]his approach uses a very small amount of the available data in an amplification curve. In addition, the assignment of the threshold value is highly subjective and is subject to conscious or unconscious bias. More of the available data could be used objectively by applying non-linear curve fitting techniques to the data in an amplification

curve.” By teaching alleged disadvantages of choosing a threshold value and determining the cycle number when the standard or unknown crosses that threshold, Wittwer in fact, *teaches away* from Applicant’s claims. Applicants remind the PTO that teaching away is indicative of non-obviousness. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.* 220 USPQ 303 (Fed. Cir. 1983); MPEP § 2141.02; *In re Hedges* 228 USPQ 685 (Fed. Cir. 1986); MPEP § 2145.

Further, dependent claims 2-6, 15 and 19-26 recite calculating the amplification efficiency from a non-linear continuously differentiable function. Wittwer does not teach or suggest calculating the amplification efficiency from a non-linear continuously differentiable function. The PTO alleges determining a non-linear continuously differentiable function is *inherently* taught in Wittwer (*see* the last 2 lines of page 4). Applicants respectfully remind the PTO that a *prima facie* case of obviousness of claims 2-6, 15 and 19-26 cannot be based on inherency. As discussed in Section A, consideration of inherency is not relevant to obviousness. In addition, even when trying to establish anticipation by “relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the prior art.” *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original); MPEP § 2112. Applicants submit that not only has the PTO erroneously relied on inherency to establish obviousness, but that it has further failed to provide any basis in fact and/or technical reasoning to reasonably support its determination.

In the instant Office Action, however, the PTO, alleges that several sections of Wittwer teach or suggest elements of claims 1-8, 15 and/or 18-30. Applicants respectfully submit that because Wittwer does not teach or suggest (1) a method of determining amplification efficiency as a function of the amount of nucleic acid; or (2) a method of determining amplification efficiency based on the determination of a cycle number at which a threshold is exceeded, the paragraphs and figures of Wittwer cited by the PTO cannot teach or suggest each and every element of independent claims 1 or 18.

First, the PTO alleges that column 41, lines 43-46, of Wittwer teaches “a method for determining the efficiency of the amplification” (*see* page 4, second full paragraph of the instant Office Action). The PTO, citing example 19 of Wittwer, states that the “amplification efficiency can be rigorously determined by integrating the melting peak data as in example 16.” As discussed above, neither example 19 nor example 16 teach or suggest a method for determining amplification efficiency as a function of the amount of nucleic acid

or a method of determining amplification efficiency based on the determination of a cycle number at which a threshold is exceeded. Example 19 or 16 might, at best, suggest calculation of amplification efficiency from a melting curve analysis, *i.e.*, from a fluorescence vs. temperature plot. The melting curve analysis, however, in no way teaches or suggests a method of determining amplification efficiency as a function of the amount of nucleic acid from a copy number vs. cycle number function. Accordingly, neither example 19 nor example 16 teaches or suggests each and every element of independent claims 1 or 18.

Next, the PTO alleges that the abstract, column 13, line 65, to column 14, line 32, examples 7, 8 and figure 44 of Wittwer teach a method for determining amplification efficiency. Applicants note that not one of the above-enumerated sections even contain the word “efficiency,” let alone “amplification efficiency.” Applicants further note that the Wittwer Abstract teaches a method of determining the concentration of a nucleic acid product, not a method of determining amplification efficiency. Column 13, line 65, to column 14, line 32, teach a method of monitoring amplification of a selected template and the determination of whether the selected template is amplifiable, not a method of determining amplification efficiency. Examples 7 and 8 of Wittwer teach the benefits of cycle-by-cycle monitoring of PCR, and the advantages and disadvantages of various fluorescence techniques, not a method of determining amplification efficiency. Examples 7 and 8 are completely silent with respect to any possibility of calculating an amplification efficiency. Figure 44 teaches melting peaks for CFTR and neu fragments. Figure 44 does not teach or suggest a method of determining amplification efficiency of a nucleic acid. Figure 44 discloses the results of a melting curve experiment and is completely silent with respect to any possibility of calculating amplification efficiency. Accordingly, none of the abstract, column 13, line 65, to column 14, line 32, examples 7, 8 or figure 44 of Wittwer teach or suggest a method for determining amplification efficiency.

Further, the PTO cites figure 44 as allegedly teaching amplification of a nucleic acid under defined conditions, measuring the amplification in real time and setting a “defined signal threshold value.” As discussed above, not only does Wittwer not teach setting a threshold value, it *teaches away* from setting threshold values and using the cycle number when the standard or unknown crosses that threshold (column 33, lines 22-31).

Next, the PTO cites figure 44 and examples 7, 8 and 16 as allegedly teaching the determination of “the cycle number for *each dilution* at which the signal threshold value is exceeded.” As discussed above, Wittwer *teaches away* from setting threshold values and

using the cycle number when the standard or unknown crosses that threshold. Further, as the PTO itself acknowledges, Wittwer does not teach or suggest dilutions of the nucleic acid.

Further, the PTO contends that column 33, line 10, to column 34, line 52, as well as figures 15-17 and 42 of Wittwer *inherently* teach “determining a non-linear continuously differentiable function of a logarithm of copy number of target nucleic acid used for the amplification as a function of the cycle number at the signal threshold value is exceeded.” As discussed above, Applicants submit that the PTO cannot establish a *prima facie* case of obviousness based on inherency and that too with mere conclusory statements unsupported by any basis in fact and/or technical reasoning. Further, as discussed above, Wittwer *teaches away* from using the cycle number when the standard or unknown crosses that threshold. Moreover, the phrases “continuously differentiable” nor “differentiable function” do not occur *anywhere* in Wittwer.

Contrary to what the PTO cites, figures 15-17 teach the different signals generated with different fluorescence techniques: fluorescence from double strand dyes (figure 15); 5'-exonuclease probes (figure 16); and fluorescence from adjacent hybridization probes expressed as a ratio of Cy5 to fluorescein fluorescence (figure 17). Figure 42 teaches a correlation between the area under the melting peak and the amount of specific product (*see* column 41, line 64-66). These figures do not teach or suggest, inherently or otherwise, determining a continuously differentiable function of a logarithm of copy number of target nucleic acid used for the amplification as a function of the cycle number at the threshold value is exceeded.

The PTO also cites the abstract, column 12, line 43, to column 13, line 64, and example 16 as allegedly teaching a method for the absolute quantification of a nucleic acid by *inter alia*, determining amplification efficiencies of the target nucleic acid. As discussed above, the Wittwer Abstract teaches a method of determining the concentration of a nucleic acid by, *inter alia*, determining *a rate constant of hybridization*, not by determining amplification efficiency. Further, example 16 as well as column 12, line 43, to column 13, line 64, teach a method of determining the concentration of a nucleic acid by, *inter alia*, monitoring the fluorescence as a function of temperature to result in a melting curve, converting the melting curve to a melting peak and determining the amount of the nucleic acid from the melting peaks. As discussed above, while these sections may teach the quantification of a nucleic acid, they certainly do not do so by teaching or suggesting the

determination of amplification efficiencies of a target and/or reference nucleic acid as recited in the instant claims.

Brown does not remedy the many deficiencies of Wittwer. Brown does not teach a method of determining amplification efficiency of a target nucleic acid as a function of the amount of target nucleic acid, nor does it teach a method of determining amplification efficiency based on the determination of the cycle number at which amplification, as measured in real-time, exceeds a threshold is determined for dilutions of the nucleic acid.

While Brown might teach preparation of terminal dilutions of genomic nucleic acid, Brown does not teach *any* method of determining amplification efficiency. Instead, Brown discloses methods “for determining the existence and/or initial concentration of a target nucleic acid in samples of about 1 microliter or less.” *See* Brown, column 4, lines 64-67. In one embodiment, the method is carried out “by conducting replicate polymerase chain reactions on a set of terminally diluted or serially smaller samples and counting the number of positive polymerase chain reactions yielding specific product.” *Id.* at column 5, lines 38-43. Thus, like Wittwer, Brown does not teach a method of determining amplification efficiency of a nucleic acid as a function of the amount of the nucleic acid. Furthermore, Brown, like Wittwer, also does not teach or suggest a method of determining amplification efficiency based on the determination of the cycle number at which a threshold is exceeded. Applicants therefore submit that Wittwer and Brown, alone or in combination, do not teach each and every element of independent Claims 1 or 18.

Further, Applicants respectfully submit that the PTO has failed to provide any suggestion or motivation to combine Wittwer and Brown. The PTO asserts that “it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the preparation of a dilution of the target nucleic acid . . . of Brown *et al.* in the method of sampling, amplifying and quantifying segment of nucleic acid of Wittwer *et al.*” Applicants respectfully remind the Examiner that in order to make out a *prima facie* case of obviousness there must be some suggestion or motivation, either in the references or in the knowledge available to one of ordinary skill in the art to modify the references or to combine the reference teachings and that there must be some reasonable expectation of success. The teaching or suggestion and the expectation of success must both be found in the prior art and not based on Applicant’s disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991). Applicants submit that, contrary to what the PTO asserts, the PTO has provided no motivation to combine Wittwer and Brown.

The PTO cites Brown, column 4, lines 23-26 and column 21, lines 1-3 of Wittwer as motivation to combine Wittwer and Brown. The cited lines from Brown state that there is a need for performing multiple different amplification and detection reactions in parallel on a single specimen and for economizing usage of reagents in the process. Applicants submit that this is the motivation provided in Brown, based on the art discussed in its “Background of the Invention” section, for its *own* invention. The motivation cited by the PTO in Brown, column 4, lines 23-26, is *completely fulfilled by Brown* itself. It is Brown, and not Wittwer that “perform[s] multiple different amplification and detection reactions in parallel on a single specimen.” Applicants therefore submit that the reasons cited by the PTO would not motivate one of skill in the art to combine Brown with *any* other reference, much less Wittwer.

Further, the cited lines from Wittwer state that with rapid cycling the required times for amplification are reduced and specificity is improved. Applicants submit that the PTO is reading these lines out of context and that the “rapid cycling” referred to in these lines is rapid temperature cycling (*see* the earlier part of this paragraph at the end of column 20) and is an improvement used in Wittwer itself and has nothing whatsoever to do with the instant invention. Accordingly, Applicants submit that the Patent Office has failed to meet the burden of demonstrating motivation to combine the teachings of the references. Further, as discussed above, neither Wittwer nor Brown, alone or in combination, teaches or suggests each and every element of independent Claims 1 or 18 or Claims 2-8, 15 and 19-30 that depend therefrom.

Since neither Wittwer nor Brown, alone or in any combination, teaches or suggests, for instance, a method of determining amplification efficiency as a function of the amount of target nucleic acid or based on the determination of a cycle number at which a threshold is exceeded, as recited in independent claims 1 and 18, the PTO’s combination of references fails to teach or suggest each and every element of independent claims 1 and 18. Since claims 2-8, 15 and 19-30 ultimately depend from Claims 1 or 18, the combination of references is also not sufficient to establish a *prima facie* case of obviousness against claims 2-8, 15 and 19-30. Applicants therefore respectfully request that the rejection of claims 1-8, 15 and 18-30 under 35 U.S.C. § 103(a) be withdrawn.

2. Wittwer and Brown, Alone or in Combination, Do Not Teach or Suggest Each and Every Element of Claims 9-14 and 16-17

Applicants respectfully submit that the references cited by the PTO are not sufficient to establish a *prima facie* case of obviousness against claims 9-14 and 16-17 because neither Wittwer nor Brown, alone or in combination, teaches or suggests each and every element of claims 9-14 and 16-17.

Independent claims 9 and 10 recite methods for quantification of a target nucleic acid relative to a reference nucleic acid standardized with a calibrator sample. The methods comprise the determining cycle numbers (Cp) at which signal threshold values are exceeded for dilutions of the target nucleic acid and the reference nucleic acid to determine continuously differentiable functions relating the Cp values to the logarithm of the amount of target or reference nucleic acid. The methods further comprise measuring the Cp values of the reference nucleic acid in a sample to be analysed and in a calibrator sample and using the continuously differentiable functions to calculate the ratio of target nucleic acid to reference nucleic acid.

Wittwer does not teach or suggest each and every element of independent claims 9 or 10. Wittwer neither teaches nor suggests the use of a calibrator sample or the determination of the ratio of the two quotients as a measure for the original amount of target nucleic acid contained in the sample. Instead, Wittwer teaches the quantification of a nucleic acid by determining the area under a melting curve (*see* example 16). Applicants remind the PTO that while other parts of Wittwer (not example 16) may teach quantification of an unknown nucleic acid relative to a *reference* sample, this is not the same as standardization with a *calibrator* sample as recited in independent claims 9 and 10.

Further, as discussed above, Wittwer does not teach or suggest quantification of a target nucleic acid by *inter alia*, determination of a cycle number at which a signal threshold is exceeded for each dilution of the target nucleic acid. In fact, Wittwer *teaches away* from choosing “a ‘threshold value’ of the signal and then [using] the cycle number when the standard or unknown crosses that threshold” (*see* column 33, lines 22-31). By teaching the disadvantages of choosing a threshold value and determining the cycle number when the target nucleic acid crosses that threshold, Wittwer teaches away from the method recited in independent claims 9 and 10. Applicants remind the PTO that teaching away is indicative of non-obviousness. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.* 220 USPQ 303 (Fed. Cir. 1983); MPEP § 2141.02; *In re Hedges* 228 USPQ 685 (Fed. Cir. 1986); MPEP § 2145. Further,

none of the sections of Wittwer cited by the PTO teach or suggest standardization with a calibrator sample.

The PTO cites example 16 and column 8, line 40, to column 9, line 19, as allegedly teaching inherently a calibrator sample and the “determination of the ratio of the two quotients as a measure for the original amount of target nucleic acid contained in the sample.” As discussed in Section A above, Applicants submit that the PTO cannot establish a *prima facie* case of obviousness based on inherency. Applicants respectfully submit that not only has the PTO erroneously relied on inherency to establish obviousness, but that it has further failed to provide any basis in fact and/or technical reasoning to reasonably support its determination. Furthermore, Applicants note that the words “calibrator” and “quotient” are not found *anywhere* in Wittwer. In addition, as discussed above, while example 16 may teach the quantification of a nucleic acid by determining the area under a melting curve, it does not teach the use of a calibrator sample or the determination of a ratio of quotients. Further, the section of Wittwer from column 8, line 40, to column 9, line 19, has nothing whatsoever to do with a calibrator sample or a ratio of quotients. Instead, the cited section teaches detecting a difference at a selected locus in a first nucleic acid as compared to a second nucleic acid (*see* column 8, lines 40-42 and column 9, lines 16-19).

Brown does not remedy the many deficiencies of Wittwer. As discussed above, Brown does not teach or suggest determination of a cycle numbers at which a signal threshold value is exceeded for each dilution of the target nucleic acid and the reference nucleic acid, as recited in claims 9 and 10. Furthermore, Brown, like Wittwer, also does not teach or suggest the use of a calibrator sample or the determination of the ratio of the two quotients as a measure for the original amount of target nucleic acid contained in the sample. Accordingly, Applicants submit that neither Wittwer nor Brown, alone or in combination, teaches or suggests each and every element of independent claims 9 and 10.

The PTO has further alleged that Wittwer and/or Brown teach some elements of dependent claims 11-14 and 16-17. The PTO contends, for example, that example 14 of Wittwer teaches the detection of amplified nucleic acid “with the aid of at least one fluorescent-labeled hybridization probe selected from SybreGreen I [sic]” and that Brown teaches the detection of amplified nucleic acid “with the aid of at least one fluorescent-labeled hybridization probe selected from TaqMan probes.” Applicants respectfully submit that Wittwer or Brown, alone or in combination, cannot teach or suggest each and every

element of dependent claims 11-14 and 16-17 because the PTO has not made out a *prima facie* case of obviousness against independent claims 9 or 10 on which these depend.

Since neither Wittwer nor Brown, alone or in any combination, teaches or suggests, for instance, the determination of cycle numbers at which signal thresholds are exceeded for dilutions of the target nucleic acid and the reference nucleic acid or the use of a calibrator sample as recited in Claims 9 and 10, the PTO's combination of references fails to teach or suggest each and every element of independent Claims 9 and 10. Since Claims 11-14 and 16-17 ultimately depend from Claims 9 and/or 10, the combination of references is also not sufficient to establish a *prima facie* case of obviousness against Claims 11-14 and 16-17. Applicants therefore respectfully request that the rejection of Claims 9-14 and 16-17 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully submit that Claims 1-37 satisfy all the criteria for patentability and are in condition for allowance. Applicants request that the Examiner reconsider this application with a view towards allowance and solicit an early passage of Claims 1-37 to issuance. The Examiner is invited to call the undersigned attorney, if a telephone call could help resolve any remaining items.

No fee is believed due with this Amendment. However, pursuant to 37 CFR § 1.136(a)(3), the Commissioner is authorized to charge all required fees, fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds, LLP U.S. Deposit Account No. 16-1150 (order no. 1803-326-999).

Respectfully submitted,

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